Patient Outcomes after Radiotherapy of Prostate Cancer. Impact of Absorbed Dose and Treated Volume.

Rasmusson, Elisabeth

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Patient Outcomes after Radiotherapy of Prostate Cancer

Impact of Absorbed Dose and Treated Volume

ELISABETH RASMUSSON
DEPARTMENT OF CLINICAL SCIENCES, LUND | LUND UNIVERSITY

Elisabeth Rasmusson is a radiation oncologist working at Skåne University Hospital, Sweden, since 2007. She also has a Master of Science degree in Chemical Engineering and has previously worked in the process industry. The overall aim of this work was to investigate the outcome of radiotherapy for prostate cancer in the clinical settings. A specific aim was to study associations between radiation dose and outcome (tumour response and/or side effects).

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Impact of Absorbed Dose and Treated Volume

Elisabeth Rasmusson

LUND
UNIVERSITY

DOCTORAL DISSERTATION

which by due permission of the Faculty of Medicine, Lund University, Sweden, will be defended in the Torsten Landberg Lecture Hall, Department of Oncology and Radiation Physics on September 25th at 9.00

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Department of Radiation Sciences, Umeå University, Umeå

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Patient Outcomes after Radiotherapy of Prostate Cancer – Impact of Absorbed Dose and Treated Volume

Abstract

Backgound

Prostate cancer is the most common form of cancer in men in Sweden. Radiotherapy, including external beam radiation therapy (EBRT) and brachytherapy (BT), is important treatment alternatives to surgery and active surveillance. Precise delivery of the prescribed absorbed dose to the prostate with minimal irradiation of normal tissue, specifically organs at risk, is crucial for optimal tumour response and limited side effects. The overall aim of this work was to investigate the outcome of radiotherapy for prostate cancer in the clinical settings. A specific aim was to study associations between radiation dose and outcome (tumour response and/or side effects) when applicable.

Material and methods

The studies were based on clinical patient data.Lymphedema was studied in 22 patients treated with EBRT including large pelvic volumes in combination with high-dose-rate (HDR)-BT and hormonal therapy after lymph-node dissection. Tumour outcome was studied retrospectlively in 195 patients treated with low-dose-rate (LDR)-BT at Skåne University Hospital. Erectile dysfunction (ED) after EBRT was studied in 673 patients, treated in the HYPO-RT-PC randomised phase 3 trial comparing conventional fractionation (CF) with ultrahypofractionation (UHF). Long-term incidence of hip complications after EBRT was studied in 351 patients using outcome data from the National Prostate Cancer Datatbase, PCBaSe.

Results:

A low rate of lymphedema was found in the group of high-risk node-positive cancer patients, supporting the feasability of this extensive treatment. Excellent outcomes were found in the cohort of low-risk prostate cancer patients treated with LDR-BT showing a biochemical failure-free survival (BFFS) rate of 95.7% at 5 years with few side effects. The dose to the prostate ($D_{90\%}$) was significantly associated with BFFS. The frequency of ED was similar in the CF and UHF treatment groups. Age was the strongest predictor of severe ED followed by dose to penile bulb (PB) beeing most evident for younger patients. EQD2-corrected doses of $D_{2\%} < 50$ Gy and $D_{mean} < 20$ Gy to PB are suggested as treatement planning objectives in order to minimise ED after EBRT. No increased risk of hip fracture was found after radical radiotherpy but an increased risk of clinically relevant osteoarthritis was observed. These results indicate that osteoarthritis after EBRT is reduced by limiting the volume of the femoral heads receiving more than 40 Gy (EQD2).

Conclusions:

Toxicity was acceptable after treating pelvic nodes with EBRT. Significant associations were found between dose coverage and tumour-control in LDR-BT, between dose to PB and ED and dose to femoral head and ostearthritis, following EBRT. These findings add valuable information in the design of future radiotherapy regimens.

Key words

Prostate cancer,external beam radiotherapy, low-dose-rate and high-dose-rate brachytherapy, dose–response, side effects, lymphedema, erectile dysfunction, hip complications, ultrahypofractionation

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To my friends in heaven

Populärvetenskaplig sammanfattning på svenska

Prostatacancer är den vanligaste cancern bland män i Sverige. Varje år insjuknar ca 10 000. Sjukdomen är starkt åldersberoende och är mycket vanlig bland äldre män. Latent cancer (icke kliniskt signifikant) förekommer ofta. Sjukdomen klassificeras som låg, mellan eller högrisk baserat på Gleason summa (tumörens aggressivitet), stadium och PSA.

Val av behandling sker utifrån riskgrupp och ålder. Lågriskcancer behöver vanligtvis inte behandlas men bör följas med aktiv övervakning för patienter med mer än 15 års förväntad kvarvarande livstid. För övriga patienter finns behandlingsalternativ i form av operation eller strålbehandling. Ofta finns mer än en behandling att välja på vilket gör att biverkningsprofilen kan vara avgörande. Strålbehandling kan ges med strålkällan utanför (extern strålbehandling) eller inuti (brachyterapi, BT) kroppen. I det senare fallet appliceras strålkällan direkt i prostata antingen i form av radioaktiva jod- eller palladium-korn (LDR/seeds) eller genom att nålar sticks i prostata där en liten iridiumstrålkälla får passera (HDR). Genom BT kan en hög stråldos erhållas till en liten volym. Man kan också kombinera extern strålbehandling med BT. Så behandlar man med gott resultat ofta patienter med högrisk prostatacancer.

Prostatacancer har relativt låg strålkänslighet. Därför krävs en hög stråldos för en botande behandling. Man försöker minimera biverkningarna genom att begränsa dosen till omgivande riskorgan som t.ex. tarm och urinblåsa. För detta ändamål används riktvärden för vilka doser som kan accepteras. Dessa baseras på litteraturuppgifter och erfarenhet. Stora randomiserade studier som underlag är sällsynt.

Målet för denna avhandling är att studera biverkningar och tumörkontroll efter strålbehandling. Speciellt undersöktes samband mellan dos och behandlad volym i förhållande till tumörkontroll och biverkningar. Avhandlingen är baserad på fyra delarbeten.

Det första delarbetet omfattar 22 högriskpatienter som behandlats med lymfkörtelutrymning, hormonbehandling, extern strålbehandling av bäckenet och BT mot prostatan. Målet var att studera biverkningar efter behandlingen med speciellt fokus på lymfödem i form av bensvullnad. Patienterna undersöktes av läkare och sjukgymnast och intervjuades angående sina besvär efter en uppföljningstid på i medeltal 2,2 år. Vi fann att lymfödem var ovanligt och att majoriteten hade mycket milda besvär (förutom gällande erektil dysfunktion, vilket var förväntat). Studien stödjer fortsatt användning av dessa stora bäckenstrålfält, som undviks på vissa kliniker. En större studie med längre uppföljning skulle dock vara önskvärt.

Det andra delarbetet är en retrospektiv studie av 195 lågriskpatienter, behandlade med LDR-BT under 2004–2008 med en medeluppföljningstid på 6,2 år. Vi fann en god 5- års biokemisk recidivfrihet på 95 % samt en statistiskt signifikant korrelation mellan dos till prostata (rapporterad som $D_{90\%}$) och biokemisk recidivfrihet. Behandlingen kan rekommenderas till patienter med gynnsam prognos där aktiv uppföljning inte är lämplig.

I det tredje delarbetet studerades erektil dysfunktion hos 673 patienter strålbehandlade i den skandinaviska HYPO-RT-PC studien där patienterna randomiserades till antingen konventionell fraktionering (CF: 78 Gy/ 39 fraktioner) eller ultra-hypofraktionerad behandling (UHF: 42,7 Gy/7 fraktioner). Vi studerade två möjliga riskområden i penisroten, penisbulben och crus. Olika dos-volym variabler togs fram för att beskriva dosfördelningen i dessa riskorgan. Därefter undersöktes eventuella samband mellan dos/volym och erektil dysfunktion. Vi fann ingen skillnad i erektil dysfunktion mellan behandlingsarmarna CF och UHF. Patientens ålder var den klart viktigaste faktorn följt av dosen till penisbulben. Dos- responssambandet var tydligast för yngre patienter (<65 år). Utifrån resultaten för dessa kunde vi rekommendera dosbegränsningar till penisbulben i form av $D_{2\%}$ (nära maximum dos) på 50 Gy och medeldos på 20 Gy, vid fraktionsdosen 2 Gy.

Det fjärde delarbetet är en studie av 346 patienter behandlade med extern strålbehandling i Umeå mellan 1997 och 2002 med 16 års uppföljning. Riskorgan i bäckenet i form av höftkulor, korsben och blygdben ritades in på dosplaneringsbilderna och doser/volymer för dessa togs fram. För att ta reda på vilka patienter som diagnostiserats med höftkomplikationer användes PCBaSe, en nationell databas för klinisk epidemiologisk forskning. Jämfört med kontrollpatienter matchade på ålder och län, fann vi ingen ökad risk för höftfrakturer men en ökad risk för höftledsartros. Den kom i medeltal 7,9 år efter strålbehandlingen och var kliniskt signifikant vilket stöds av att den i 80 % av

fallen ledde till operation med höftplastik. Dos-responsanalys gav ett statistiskt signifikant samband mellan V_{40Gy} (andel av höftkulorna som fick dosen 40 Gy eller mer) och risk för höftledsartros. Medeldosen i materialet var dock låg (35,5 Gy) och vi erhöll vida konfidensintervall för sambandet. Baserat på vårt resultat och andras publicerade fynd rekommenderar vi att hålla dosen till höftkulorna under 40 Gy där detta är möjligt utan att för den skull riskera dostäckning av tumör eller för hög dos till andra mer prioriterade riskorgan såsom ändtarm.

Sammanfattningsvis visar de genomförda studierna på olika metoder för att öka kunskapen för dos-respons samband i kliniken. Moderna dosplaneringsmetoder ger ökade möjligheter till dosbegränsningar till riskorgan. Nya (hypofraktionerade) behandlingar ger ökade krav på att verifiera våra riktvärden för doser till riskorgan. Utrymmet för fortsatt arbete inom området är därför stort.

Abbreviations and definitions

ADT	androgen deprivation therapy
AS	active surveillance
BED	biologically effective dose
BFFS	biochemical failure free survival
bNED	biochemical no evidence of disease
BT	brachytherapy
CF	conventional fractionation, i.e. 1.8-2.0 Gy per fraction
CT	computed tomography
CTC	common toxicity criteria
CTCAE	common toxicity criteria adverse events
CTV	clinical target volume
3D-CRT	three-dimensional conformal radiation therapy
EBRT	external-beam radiotherapy
ED	erectile dysfunction
EORTC	European Organization for Research and Treatment of Cancer
ePLND	extended pelvic lymph node dissection
EQD2	equivalent dose in 2-Gy fractions
GU	genitourinary
HDR	high dose rate
HR	hazard ratio
IGRT	image-guided radiation therapy

IMRT	intensity-modulated radiation therapy
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
LENT/SOMA	late effects in normal tissue/subjective objective management analytic
LDR	low dose rate
LQ model	linear-quadratic model
MRI	magnetic resonance imaging
NTCP	normal tissue complication probability
NVB	neurovascular bundles
OAR	organ at risk
PB	penile bulb
PCSS	prostate cancer symptom score
PET	positron emission tomography
PDE5i	phosphodiesterase type 5 inhibitor
PLNRT	pelvic lymph node radiotherapy
PROMs	patient-reported outcome measures
PSA	prostate specific antigen
PTV	planning target volume
QUANTEC	quantitative analyses of normal tissue effects in the clinic
RP	radical prostatectomy
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
SBRT	stereotactic body radiotherapy
$TD_{5/5}$	"tolerance dose", the dose that results in 5% risk of a severe complication within 5 years after irradiation
$TD_{50/5}$	the dose that results in 50% risk of a severe complication within 5 years after irradiation

TDC	tissue dielectric constant
TRUS	trans-rectal ultrasound
UHF	ultrahypofractionation, i.e.≥ 5 Gy per fraction
VMAT	volumetric modulated arc therapy

List of Papers

This thesis is based on the following four papers which will be referred to in the text by their Roman numerals

I. Rasmusson E, Gunnlaugsson A, Blom R, Björk-Eriksson T, Nilsson P, Ahlgren G, Jönsson C, Johansson K, Kjellén E. Low rate of lymphedema after extended pelvic lymphadenectomy followed by pelvic irradiation of node-positive prostate cancer. *Radiat. Oncol.* 2013, 8:271

II. Rasmusson E, Gunnlaugsson A, Kjellén E, Nilsson P, Einarsdottir M, Wieslander E, Fransson P, Ahlgen G, Blom R. Low-dose rate brachytherapy with I-125 seeds has an excellent 5-year outcome with few side effects in patients with low-risk prostate cancer. *Acta Oncol*. 2016 Aug; 55(8):1016-21

III. Rasmusson E, Gunnlaugsson A, Wieslander E, Höglund P, Widmark A, Fransson P, Kjellén E, Nilsson P. Erectile dysfunction and absorbed dose to penile base structurers in a randomized trial comparing ultrahypofractionated and conventionally fractionated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2020 May 1; 107(1):143-151.

IV. Rasmusson E, Nilsson P, Kjellén E, Gunnlaugsson A. Long-term risk of hip complications after radiotherapy for prostate cancer – A dose-response study. Manuscript

Contents

Background

Prostate cancer

Epidemiology

Prostate cancer is the most common form of cancer in men in Sweden with about 10 000 new cases each year. The incidence escalated during the 1990s and early 2000s due to both an increase in diagnostic (prostate-specific antigen (PSA)) testing and an aging population. Although the age-specific mortality rate has decreased over the past fifteen years, about 2400 men still die of prostate cancer in Sweden each year. Latent (clinically non-significant) prostate cancer is common and the disease is strongly age dependent. The main challenge facing the health care system is to minimise mortality due to prostate cancer while avoiding overtreatment (1).

Staging and prognosis of localised disease

Localised prostate cancer is divided into risk groups based on tumour grade (Gleason score), stage and PSA value. Stage is based on the TNM-classification (8th Edition of the Union for International Cancer Control, UICC, TNM classification of malignant tumours 2017).

The risk of death due to prostate cancer in 10-15 years after diagnosis without curative treatment is less than 10% in low-risk patients and 20% in intermediate-risk patients. For high-risk patients, the risk of death in five years is 20-30% (1). Thus, many patients have a long life expectancy and side effects of treatments cannot be neglected.

Node-positive cancer

The spread of disease to the pelvic lymph nodes is common in high-risk patients, of whom at least 20% have lymph node metastases. According to the Swedish National Health Care Programme for Prostate Cancer, high-risk patients and some intermediate risk patients should be examined with either pelvic MRI/CT or PET/CT (using radiolabelled choline or acetate). New imaging techniques such as PSMA-PET are not yet recommended in the clinical setting (1). There are no clear recommendations for the treatment of patients with limited lymph node metastases. These patients have historically been thought to harbour systemic disease. However, the results of retrospective studies have indicated the benefit of local therapies (2, 3). Lymphadenectomy in combination with radical prostatectomy, or radiation therapy of the pelvic lymph nodes in combination with androgen deprivation therapy (ADT) can be offered to selected patients, preferably in clinical studies (1).

Treatment options

The optimal treatment for individual cases depends on the risk group, the remaining life expectancy, comorbidity and patient preferences.

Active surveillance

Active surveillance (AS) has been adopted in various parts of the world for 15 years, and is now the standard of care for low-risk and selected intermediate-risk patients (1, 4). Apart from testing for PSA and repeated biopsies, modern AS programmes include MRI examination and the measurement of biomarkers as well as genetic testing (4). Definitive treatment of these patients is considered when biopsy-proven Gleason grade 5, or more than negligible grade 4 is found. Other factors indicating the need for definitive treatment are increasing PSA level, progress according to MRI or hereditary deadly prostate cancer (as BRACA-2 mutation). About 25-50% of the patients in AS programmes require active treatment within five years as a result of reclassification of the risk or increasing PSA levels (5-7).

Surgery

Definitive curative treatment can be offered in the form of surgery, i.e. radical prostatectomy (RP) with or without lymph node dissection. The procedure is performed using open retropubic, laparoscopic transabdominal or robot-assisted laparoscopic transabdominal surgery. Dissection of the obturator fossa nodes alone is now not clinical practice. Extended pelvic lymph node dissection (ePLND), including the obturator fossa, external and internal iliac nodes, may be indicated in high-risk patients. Lymph-node dissection increases the complication rate and the oncological benefit is uncertain (8) but provides prognostic information through more accurate staging (2).

Preservation of the neurovascular bundles (NVB) reduces the rate of post-RP urinary incontinence (9) and increases the rate of erectile function recovery, but depends on tumour location. Recovery of erectile function has been reported to be better after robot-assisted surgery than open surgery for low-intermediate-risk tumours, but not for high risk tumours (10). In a prospective study of 531 men, it was found that age, degree of nerve-bundle preservation, preoperative erectile function and preoperative hypertension influenced erectile function after RP (11). In this study, 70% and 43% of the patients treated with bilateral and unilateral NVB preservation, respectively, regained baseline erectile function with or without PDE5i (phosphodiesterase type 5 inhibitor), while only 4% of patients treated with non-NVB preservation (65% of all patients) regained erectile function.

Radiotherapy

Radiotherapy (RT) of prostate cancer can be performed as external beam radiotherapy (EBRT), brachytherapy (BT) or a combination of both.

External beam radiotherapy

ERBT can be used to treat patients with low-, intermediate- or high-risk disease; in the last case combined with ADT. As prostate cancer is not very sensitive to radiation, several dose escalation studies have been performed in order to improve tumour control. Several randomised dose-escalation trials have reported a lower risk of biochemical recurrence in the prescribed dose interval 74-80 Gy using conventional 2 Gy fractions than with former standard-of-care schedules with total doses in the range of 64-70 Gy (12-15).

Based on the high radiation-fraction sensitivity of prostate cancer several trials have been performed using hypofractionated RT have been performed as a means of increasing the therapeutic ratio. Hypofractionation is generally categorised as moderate hypofractionation or ultrahypofractionation (UHF) with fraction sizes in the range of 2.4-3.4 Gy and ≥5 Gy, respectively. The result of published studies indicate that moderate hypofractionation is safe and results in disease control comparable to that accomplished with CF and the clinical practice has thus be changed at many RT centres (16).

UHF RT for prostate cancer is not yet the standard of care, although many studies are ongoing, and the results obtained so far seem promising (16). Five-year outcomes from a large randomised UHF study, the Scandinavian HYPO-RT-PC trial, have recently been reported (17). The UHF schedule in this trial (7 fractions of 6.1 Gy each) was found to be non-inferior to CF regarding failure-free survival, with similar late side effects in the treatment arms. Stereotactic body radiotherapy (SBRT) is a variant of UHF in which typically 1-5 fractions are precisely delivered to a target using either a conventional linear accelerator or a robotic-based radiosurgery system. Prostate SBRT has been shown in multiple prospective phase I-III trials and single institution reviews to be both safe and effective for the treatment of intermediate-risk patients (18).

MRI is recommended for structure delineation for treatment planning due to its high soft-tissue contrast compared to CT. Dose planning with MRI as the only imaging modality has been studied but the benefit of treating patients with this method has yet not been fully evaluated (19). Intensity-modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT) have become the standard RT techniques for the treatment of prostate cancer, as it allows the delivery of highly conformal radiation dose distributions. The prostate is not a fixed organ and can change position slightly inside the body depending on how full or empty the lower bowel (rectum) and bladder are. To obtain good dose coverage of the target volume with small CTV (clinical target volume) to PTV (planning target volume) margins, image-guided techniques based on e.g. implanted markers have been developed.

There is no strong evidence of the benefit of adding EBRT of the pelvic lymph nodes (PLNRT) (20, 21). Studies suggest that patients with limited disease (≤4 positive lymph nodes) benefit from this treatment (22) and that the toxicity is acceptable (22, 23). Results from the NRG Oncology/RTOG 0534 SPPORT Trial comparing EBRT of the prostate bed with and without ADT and with addition of PLNRT were presented at ASTRO 2018 (24), and showed significant

improvement in freedom from progression with addition of PLNRT in the post-operative setting, however these findings have not yet been published.

Brachytherapy

BT is a form of radiotherapy in which the radiation source is positioned inside or next to the volume requiring treatment, in this case the prostate. BT can be delivered at a high dose rate (HDR) or a low dose rate (LDR). Both methods requires that the patient be anaesthetised for insertion of the sources. Trans-rectal-ultrasound (TRUS) is used for guidance during implantation. The main organs at risk (OAR) are the urethra and the rectum. BT can be used as monotherapy or combined with EBRT. The main advantage of BT is that the irradiation affects primarily a localised volume around the radiation source, with a very steep dose fall-off. In addition, if the treated organ moves within the body during period of treatment, the radiation source should retain its position in relation to the organ. However, LDR seeds may migrate. The volume of normal tissue irradiated is relatively small compared to the use of EBRT, which facilitates dose escalation and high doses per fraction.

In LDR-BT radioactive seeds (iodine-125 or palladium-103) are permanently implanted via temporarily inserted catheters. Images are acquired, with the catheters in place using TRUS, and then transferred to a treatment planning system where the prostate and OAR are delineated. The position of the seeds along the catheters is optimised, to achieve the stipulated objectives for dose coverage and the dose to the OAR. Typically 50-90 seeds are implanted. A post-implant CT scan is commonly used for verification and optional implantation of extra seeds. The development of the method started in the mid-1980s when TRUS was developed, as this is essential in determining the optimal positions of the seeds. There are mature data supporting the use of LDR as monotherapy for low-risk patients and selected intermediate-risk patients, with disease control rates over 90% (25).

In HDR-BT the absorbed dose is delivered by an iridium-192 source via temporarily inserted catheters. Images are acquired with the catheters in place using TRUS (sometimes supplemented by MRI or CT-scan). The images are then transferred to a treatment planning system where the prostate and OARs are delineated, as described above. Anatomy-based inverse planning and manual optimisation are used to define the iridum-192 source dwell time at each position along the catheters, in order to achieve the stipulated objectives for dose coverage and dose to OARs. There is growing evidence supporting the use of monotherapy HDR-BT in patients with low-or intermediate-risk disease but this is not a standard-of-care (25). EBRT (typically 25 x 2.00 Gy) combined with HDR-BT

boost (typically 2 x 10 Gy), is an aggressive local treatment used for high-risk patients, showing good results (26, 27). Pelvic lymph nodes have been included in the EBRT target volume in some non-randomised studies with acceptable radiation toxicity (28, 29).

Androgen deprivation therapy

ADT is widely used in the palliative setting for hormone-sensitive prostate cancer. In the curative setting neoadjuvant and adjuvant ADT are combined with RT for high-risk patients as this appears to have a synergistic effect with RT by preventing DNA repair (30-32). Adjuvant ADT is sometimes given after surgery to patients with a high risk of recurrence(1).

Disease control after definitive treatment

Both surgery and RT are alternatives for definitive treatment. A few observational studies have indicated improved survival following surgery (RP) compared to RT. However, this could be due to selection bias, as the patients treated with RT are older and have more comorbidity (33). The outcome after 10 years has been reported in a randomised study, the ProtecT-trial, including 1643 patients comparing AS, surgery and RT (with neo-adjuvant and concomitant ADT) for low- and intermediate-risk patients (6). It was found that the prostate-cancer-specific mortality was low (approximately 1%) irrespective of the treatment, with no statistically significant differences. AS was associated with a higher incidence of disease progression and metastases, and 55% of the AS patients received local treatment within 10 years (19% in 9 months).

In high-risk patients, treatment with EBRT+BT combined with ADT has been reported to be associated with significantly lower prostate-cancer-specific mortality and longer time to distant metastases compared to EBRT with ADT or RP (26, 34, 35). However, there is a risk of bias as patients receiving BT are selected based on suitability for anaesthesia, having a maximum prostate volume of 50 cm^3 and not having lower urinary tract symptoms i.e. healthier patients. The BT boost can be delivered with either LDR or HDR (36). The ASCENDE-RT trial, a randomised trial comparing 46 Gy EBRT to the pelvis followed by either EBRT to the prostate up to 78 Gy or LDR BT-boost (minimal peripheral dose of 115 Gy) for intermediate- and high-risk prostate cancer revealed the same advantage of BT boost. Men randomised to the LDR-BT boost were twice as likely to be free of biochemical failure at a median follow-up of 6.5 years (37).

Comparison of side effects after definitive treatment

Observational and randomised data regarding urinary, erectile, and bowel function indicate few long-term (>5 years) differences between surgery and RT, although short-term urinary continence and erectile function appeared to be worse following surgery, and short-term urinary bother and bowel function seemed to be worse following RT (1, 38). Other complications such as hospitalisation, the need for urological, recto-anal, and other major surgical procedures, and secondary cancers have been shown to be more common among men treated with RT (38). This could be due to bias as RT patients are older and have more comorbidity. ADT, frequently co-administered with RT, contributes to additional morbidity for example, cardiovascular disease, osteoporosis, sexual dysfunction and depression (38).

Side-effects 10 years after treatment were studied in the ProtecT-trial (39). Urinary incontinence was found to be significantly increased following surgery, compared to AS and RT. Surgery (RP) and RT both reduced erectile function in the first year after treatment with a larger decline for RP. At 6 years 29% of RT patients and 15% of RP patients reported erections sufficient for intercourse, compared to baseline values of 63% and 66%, respectively. The erectile function for the AM patients declined gradually over time to 35% at 6 years, compared to baseline value of 68%. The differences were statistically significant. These results reflect the influence of both treatment and aging.

A partly randomised, prospective cohort study, CEASAR (40), confirmed a greater decline in sexual function scores after 3 years' follow-up in patients receiving RP than in EBRT patients for the 25% of men with excellent baseline scores. The outcome for the patients with somewhat lower baseline functions was poor, regardless of whether they underwent RP or EBRT. Urinary incontinence scores were worse following RP than EBRT or AS. Urinary irrigation scores improved in RP patients. No clinically significant differences in bowel or hormone function were noted beyond 12 months

LDR-BT is reported to be associated with increased genitourinary toxicity compared to EBRT, HDR-BT and RP (25, 27, 41). The results of non-randomised studies (and one randomised study on RP compared to BT) suggest that LDR-BT might be associated with a lower risk of ED than surgery or EBRT (41-44). The ASCENDE-RT trial (45) reported that LDR-BT boost led to a higher incidence of both acute and late GU morbidity than EBRT boost, the latter being manifested as urethral stricture in about 50% of the cases. No difference in the frequency of ED were reported.

Concerning secondary cancer, a meta-analysis of studies revealed a 65-80% increased risk of cancers of the bladder, colon and rectum after RT, compared with the risk in those not exposed to RT but the reported absolute rates were low (1-4%) (46). Long-term follow-up (12 y) in a study comparing EBRT +ADT to ADT, SPCG 07, (47) revealed a 20% increase in all secondary cancers, and a 250% increase in bladder cancer. However, this was outweighed by the improved overall survival of RT patients.

Radiobiology

Tumour growth and radiation sensitivity

The growth rate of a tumour is determined by the rates of cell production and cell loss. Cell production is determined by the proportion of actively dividing cells (the growth fraction) and the cell-cycle time. The growth fraction can be measured in tumour biopsies using, for example the Ki67 labelling index (the ratio of cells staining positively for the cell-cycle protein Ki67) (48).

In prostate cancer the Ki67-index is usually low, with mean values of less than 10%, which can be compared with 30% for head and neck cancer and 37% in non-small-cell lung cancer (48, 49). The use of the Ki67 index has not been established in clinical practice for prostate cancer, but has been suggested to be a predictive marker of biochemical/clinical recurrence after RT independently of established prognostic factors, including the Gleason score (50).

The cell-cycle time is more difficult to measure, but has been determined to be slightly shorter in adenocarcinoma (the most common cancer in the prostate) than in squamous-cell carcinoma or melanoma. The cell-loss factor in malignant tumours is quite high, often greater than 80%, and the value for prostate cancer has been reported to be as high as 97%. (48).

Radiation sensitivity is the relative susceptibility of cells or tissues to the damage caused by radiation. In general, cell radiosensitivity is directly proportional to the rate of cell division and inversely proportional to the degree of cell differentiation. Prostate cancer is usually well-differentiated and slow-growing, and is considered to have a fairly low radiosensitivity, consequently requiring a high absorbed dose for tumour control (48).

Fractionation

Cell survival and the linear-quadratic model

A cell-survival curve describes the relationship between the fraction of surviving cells (S) and the radiation dose (D) (Figure 1). When plotted on a log-linear scale the curve is typically non-linear and the initial part is often termed the "shoulder". It can be mathematically fitted by a second-order (linear-quadratic) equation such as the linear-quadratic or LQ-model, i.e.

$$-\ln(S) = \alpha \cdot D + \beta \cdot D^2$$

where and are constants. The degree of curvature (shoulder) of the cell-survival curve can be conveniently described by the quotient of the constants, α/β (unit Gy).

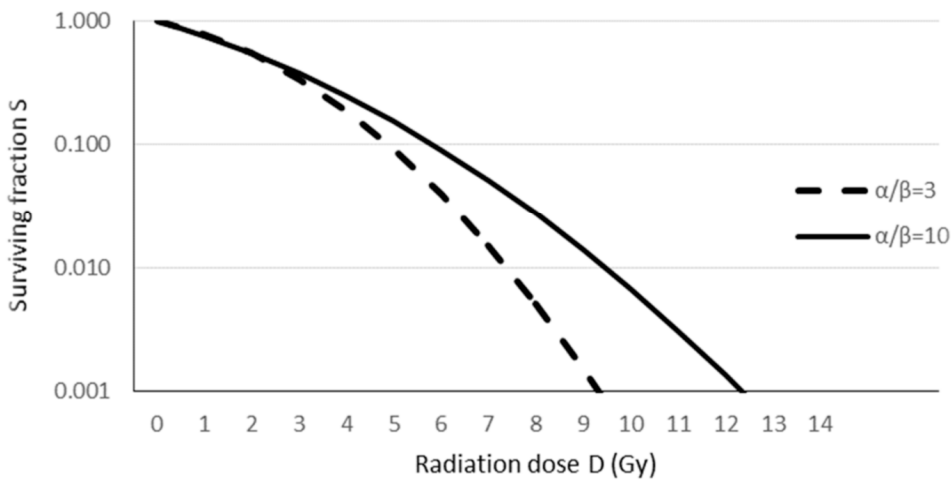

Figure 1. Schematic cell survival curves for α/β=3 Gy and 10 Gy both with surviving fraction of 0.55 at 2 Gy.

The LQ-model is widespread in both experimental and clinical radiobiology. DNA double-strand breaks are believed to be the primary mechanism leading to cell death. The linear component (αD) is often referred to as being the result of single-track events which are non-repairable, while the quadratic component (βD^2) may result from two-track events which are repairable. Cell lines with a high α/β value have

nearly-constant rates of cell killing with increasing dose, while cell lines with a low α/β value show a pronounced curvature, the rate of cell killing per unit dose being higher at higher doses. The dose range in which the LQ model is valid has been debated but according to Joiner (48) seems to work extremely well up to 5-6 Gy/fraction. Brenner suggests that the model is reasonably valid up to about 10 Gy/fraction, and could possibly be used up to 18 Gy/fraction (51). The basic LQ model does not take the overall treatment time into account. For rapidly proliferating cells (early responding tissues) a correction should be considered for treatment time.

For fractionated irradiation with complete repair and negligible proliferation between fractions, the shape of the cell survival curve is repeated for each fraction. Hence, the cell survival after *n* fractions, each with a dose, *d*, and total dose $D = n \cdot d$ can be written:

$$-\ln(S) = n(\alpha \cdot d + \beta \cdot d^2) = D \cdot (\alpha + \beta \cdot d)$$

The biologically effective dose for tumour/tissue effects.

The LQ model can also be applied to the effects (E) of radiation on tumour or tissues. Assuming that *E* is proportional to the logarithm of the surviving fraction of cells responsible for the tissue effect, i.e. $E = -\ln(S)$, the LQ-model for fractionated irradiation can be written:

$$E = D \cdot (\alpha + \beta \cdot d)$$

Fowler (52) defined the concept of the biologically effective dose (*BED*) as E/α for reporting the fractionation-corrected dose:

$$BED = \frac{E}{\alpha} = D \cdot \left(1 + \frac{d}{\alpha/\beta}\right)$$

Another very useful concept for reporting the fractionation-corrected dose is the concept of the equivalent dose at 2 Gy per fraction (*EQD2*). If an arbitrary fractionation schedule of *n* fractions each with a dose *d* to a total dose *D* has the same *BED* as a 2-Gy schedule with total dose *EQD2*, i.e. they are iso-effective for a specific endpoint, then

$$EQD2 = D\frac{d + {}^{\alpha}/_{\beta}}{2 + {}^{\alpha}/_{\beta}}$$

where α/β is the fractionation sensitivity for the tissue effect studied.

As mentioned above, the LQ model assumes that the interval between fractions is sufficiently long to allow full recovery between fractions (usually at least 6 hours). If this assumption is not valid, a correction must be made for incomplete repair. The influence of incomplete repair is determined by the repair half-time ($T_{½}$) of the cells in the irradiated tissue (48).

Fractionation sensitivity

The relationship between the total dose and the dose per fraction for the tumour and the surrounding normal tissues, i.e. the fractionation sensitivity (α/β) is important for the optimisation of RT schedules. With knowledge of α/β the LQ model (or *BED* or *EQD2* equations) can be used to calculate such relationships. The steepness and curvature of the curves are determined by α and β. For early-responding normal tissue the quotient α/β is high (typically 7-20 Gy), while a low value of α/β (0.5-6 Gy) is characteristic of late-responding normal tissue. Many tumours, such as squamous cell carcinomas of the head and neck and lung, have a fractionation response similar to that of early responding tissues i.e. a high α/β ratio. These tumours are suitable for hyperfractionation.

There is now strong evidence that prostate cancer has a low α/β value, as low as 1-2 Gy (53-55), i.e. even lower than the typical α/β of 3 Gy for late responding tissues. These results confirm the original findings of Brenner and Hall (56). There are also indications that there are no significant differences in α/β between different risk groups of prostate cancer (57). These results support the use of hypofractionation for prostate cancer to increase the therapeutic ratio for these tumours.

The dose-rate effect

Continuous low-dose-rate irradiation is equivalent to multiple infinitely small fractions, given without any radiation-free intervals and cell damage and repair takes place simultaneously. Most human tissues are less affected by irradiation as the dose rate is reduced probably as a result of maximum tissue recovery/repair. The repair half time of prostate cancer has been suggested to be 0.5-2.0 h (58,

59). As the dose rate is reduced the β-term is reduced (due to repair) and the cell survival curve become straighter.

In some slow-growing cell lines, however, an inverse dose-rate effect has been described, with an increase in steepness of the survival curve when the dose rate is very low. A possible explanation of this could be that the low dose rate allows the cells to progress through the cell cycle and accumulate in G2 (the gap between DNA synthesis and mitosis, when the cell continues to grow and produce new proteins), a more radiosensitive phase (60). The value of this effect in clinical practice is unclear.

The pathogenesis of side effects after RT

Radiation treatment may lead to loss of function of normal tissue due to damage to the parenchymal cells in the organ and/or damage to the stroma and vasculature. The radiation-induced effect depends on the radiation quality, dose, dose rate and radiosensitivity of the affected tissue. Healing can be achieved by regeneration, replacement with the same cell type or repair with replacement by other cell types e.g. fibrosis. The response is divided in early and late effects by definition at 90 days after treatment (48, 60).

Early side effects are observed during and shortly after a course of RT. They are seen in tissues with high proliferative activity, such as the skin and mucosa. The symptoms are due to loss of proliferative capacity accompanied by inflammatory changes. Healing is usually complete, but sometimes leads to consequential late side effects. Examples of early side effects after RT of prostate cancer are cystitis and proctitis, caused by injury to the endothelial cells (48, 60).

Late side effects become clinically apparent in the affected organ after months or years. They are irreversible and sometimes progressive. The pathogenesis is complex involving cell death, differentiation of fibroblasts and loss of capillaries as well as the immune system. The clinical consequences depend on the architecture of the organ and the volume irradiated. The latent time for late radiation effects is inversely dependent on dose, i.e. the higher the dose the shorter the time to clinical manifestation of the effect. Examples of late side effects after RT of prostate cancer are ED, chronic proctitis, urethral stricture and hip osteoarthritis. Vascular radiation effects such as occlusion of capillaries and sclerosis of arterioles, probably interact with other mechanisms such as fibrosis for several of the end points (48, 60).

Dose–response relationships

Dose–response curves and the therapeutic ratio

A dose–response relationship is present when the risk of a specific biological effect increases (in frequency, severity or both) significantly with increasing dose. The relation between radiation dose and the frequency of a specific end point is often presented graphically as a sigmoid-shaped dose–response curve. The endpoint may be cancer control (tumour control probability, TCP) or side effects (normal tissue complication probability, NTCP). The aim of RT is to separate the TCP and NTCP curves as much as possible, i.e. to maximise the so called therapeutic window or therapeutic ratio. Optimisation of the dose distribution on the target and OAR, as well as the fractionation schedule, are examples of how the therapeutic ratio can be increased. Another way of improving the therapeutic window may be via radiosensitisers and/or radioprotectors (48). The NTCP for a specific endpoint does not only depend on the dose and fractionation schedule but also on the fractional volume of the OAR receiving a specific dose. Several mathematical models have been developed describing these relationships, the most well-known being the so- called Lyman-Kutcher-Burman model (61) originally applied to the clinical tolerance data published by Emami et al.(62).

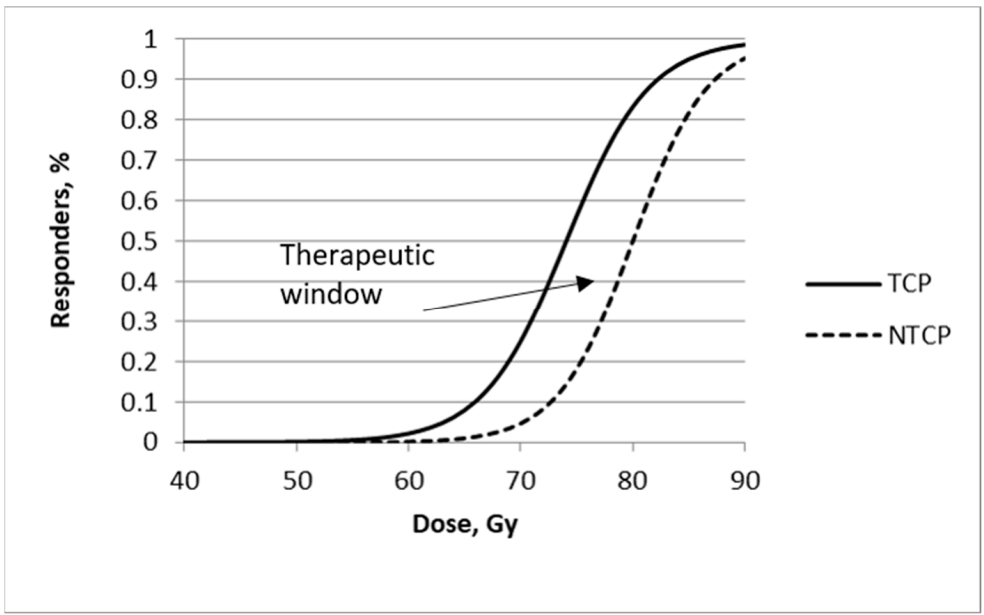

Figure 2. Schematic dose–response curves

TCP for prostate cancer

The conventionally fractionated EBRT dose-escalation trials performed during the 1990s showed a significant improvement in bNED (biochemical no evidence of disease) with increasing dose to the prostate (63-65). As discussed above there is strong evidence of a low α/β for prostate cancer. In a recent meta-analysis of randomised trials Vogelius and Bentzen investigated the dose response and fractionation sensitivity of prostate cancer (55). From the dose escalation trials included in their study, a statistically significant dose-response gradient was found for bNED but not for overall survival. Heterogeneity in the data indicated that EQD2 >80 Gy might not improve bNED.

Retrospective LDR-BT studies have demonstrated an association between the dose variable $D_{90\%}$ (the dose received by 90% of the prostate) and bNED supporting the objective of target dose coverage of BED in the range of 180-200 Gy (66-68).

NTCP, toxicity endpoints

A detailed understanding of the causes and anatomical origins of an RT- induced complication is important. Several scoring systems for toxicity have been established, such as RTOG/EORTC (69), CTCAE (70), and LENT/SOMA (71). These can sometimes be combined with underlying discrete symptom-specific data. The QUANTEC group recommended that grading schemes based on symptoms of logical clinical syndromes, rather than organ-specific collections of symptoms. (72)

A clinical grading system may not be ideal for dose–response analysis for several reasons, for example as that various symptoms from a single organ often are grouped. An example both reduced capacity of the bladder and bleeding due to local ulceration can be considered bladder injury, but they may have different dose/volume–response relationships. Another problem is that symptoms do not always originate from one specific organ, for example pelvic pain (72).

Patient-reported outcome measures (PROMs) are common in clinical studies, and standardised grading systems such as PRO-CTCAE or other validated instruments are recommended.

OAR dose-volume constraints/objectives

Dose-volume constraints/objectives for OAR are necessary tools in daily treatment planning in order to minimise the risk of side effects. However, large prospective studies on the doses to OAR and their correlation with toxicity are rare.

Many dose-volume constraints used in the clinic today are primarily based on reviews of the literature such as the QUANTEC reports published in 2010 (73, 74) which are based on pooled data from studies with different numbers of patients, patient selection criteria and endpoints. Of special interest for RT of prostate cancer are three of the QUANTEC reports on dose-volume objectives for gastrointestinal (GI), genitourinary (GU) toxicities and ED (75-77). However, dose-volume data from the 1991 compilation by Emami et al (62) are still used, especially for organs/side effects not covered by the QUANTEC report. Updated GU dose–response relationships following prostate cancer RT were published by Thor et al. in 2016 (78). A systematic post-QUANTEC review of tolerance doses for late toxicity after prostate cancer RT were published by Olsson et al. in 2018 (79). Updated dose-volume tolerances especially for GI symptoms (scare for GU and ED), based on 33 studies, are presented in this review.

More detailed information on the side effects studied specifically in the work presented in this thesis is given below.

Erectile dysfunction

Suggested mechanisms for ED include neural injury, vascular alterations and corporal smooth muscle changes. Haemodynamic measurements show significant changes in arteries and veins after RT such as venous leakage most commonly from the crus of penis (80).

Studies on erectile function after RT in relation to the dose to critical erectile structures are mainly focused on the penile bulb (PB) and crus as OAR but other OAR are probably of importance. In the QUANTEC review, Roach et al. concluded that, "the bulb might be a surrogate for yet to be determined structures" and that "it is prudent to keep the mean dose to 95% of the bulb to less than 50 Gy" (77). A lower threshold dose (mean dose of 20 Gy), has been suggested in a recent publication by the CHHiP trial group (81). Vessel-sparing RT (sparing the crus, PB and the internal pudendal artery) has shown promising results in a single-arm phase 2 trial (82). A novel OAR, the prostatic plexus, has been suggested, to be important for erectile function. The plexus lies within the prostatic fascia lateral and posterior to the prostate forming the neurovascular bundles and entering into the corpora cavernosa. The prostatic plexus gives rise to the cavernosal nerves that help control the neural input for erections. Irradiation of the prostatic plexus is unavoidable during RT of the prostate, but it has been suggested that attempts should be made to avoid hot spots in the region (83).

Use of a (hydrogel) spacer between the prostate and rectum has been reported to reduce the dose to the PB which is associated with improved erectile function. The mechanism behind PB dose reduction was unclear (84).

Bone toxicity

Adult bone and cartilage are believed to be relatively radiation resistant, although there is very little epidemiological data on the dose-response relationships. Radiation-induced femoral head/neck toxicity such as pain, fractures, cortical bone thinning and necrosis are complications that may occur after RT (85, 86). Early RT studies reported a threshold of 30 Gy for increased risk to produce irreversible damage to bone tissue and joint arthropathy (87, 88). Emami et al. suggested TD5/5 (the dose that results in 5% risk of a severe complication within 5 years after irradiation) and TD50/5 values of 52 Gy and 65 Gy to the femoral head respectively, for the end point necrosis. A small study on anal cancer showed that femoral neck volume receiving more than 40 Gy (V_{40Gy}) was predictive of clinically significant cortical thinning (86).

The incidence of symptomatic pelvic insufficiency fractures after RT for prostate cancer has been reported to be 6.8 % after 5 years, which is lower than the incidence reported for gynaecological patients (89). The cumulative incidence of hip fracture 10 years after treatment by RT has been reported to be 8.4%, compared to 2.6 % for patients treated with RP, i.e. significantly higher (90). In contrast other studies found no increase in the incidence of hip fractures after EBRT (91, 92).

Hip pain has been reported to be significantly associated with the absorbed dose to the femoral head in a study of long-term gynaecological cancer survivors. A maximal mean physical absorbed dose of 37.5 Gy to the femoral head was recommended (93).

Lower extremity lymphedema

Lower extremity lymphedema typically occurs after pelvic lymph node dissection. For gynaecological cancer postoperative RT and the number of lymph nodes dissected have been reported to be associated with lymphedema (94), but this has not been studied extensively for prostate cancer. In RTOG (Radiation Therapy Oncology Group) studies with extended-field irradiation for the treatment of prostate cancer, genital and/or leg oedema was noted in about 5% of the patients and the oedema persisted in the majority of the patients (95). The lymphedema developed only in patients with lymphadenectomy prior to RT and appeared during the first treatment year. In a more recent study, the severity and frequency

of lymphedema were studied in 43 patients (96). All these patients underwent choline-PET/CT-imaging before lymphadenectomy followed by adjuvant RT of 50Gy to pelvic nodes. Only mild cases of lymphedema were diagnosed during RT and no chronic lymphedema was observed.

Aims

The aim of the first study (Paper I) was to investigate late toxicity, focusing on lymphedema, in patients with node-positive prostate cancer treated at our hospital with ePLND followed by EBRT of the prostate, seminal vesicles and pelvic lymph nodes and HDR-BT boost to the prostate.

The second study (Paper II) was carried out to evaluate the outcome of LDR-BT of the prostate regarding tumour control and side effects for this treatment at our department, focusing on the relationship between absorbed dose and biochemical failure-free survival (BFFS).

In the third study, the relationship between the absorbed dose to penile-base structures and erectile dysfunction (ED) was investigated in patients treated in the HYPO-RT-PC phase III trial comparing conventionally fractionated (CF) and ultrahypofractionated (UHF) radiotherapy, for the treatment of intermediate- to-high-risk prostate cancer. Specifically, it was investigated whether any dose-volume objectives could be recommended to reduce the risk of ED (Paper III).

Finally, the long-term incidence of hip complications, measured as fractures, replacements, infections, and osteoarthritis, after EBRT, was compared with those in age-matched controls from the general population. Possible dose–response associations were also investigated (Paper IV)

Materials & Methods

HDR and pelvic EBRT – Clinical examination and qualitative interview of patients

A total of 26 patients with high-risk node-positive prostate cancer, treated with HDR-BT and large pelvic field irradiation with EBRT following ePLND and ADT, were invited to participate in the study. These were all the patients treated with this combination of therapies at Skåne University Hospital before 2011.Twenty-two (85%) patients agreed to participate (Paper I).

The clinical examination and the qualitative interview were performed by an oncologist. The patients were asked to fill in a standard quality of life questionnaire, the Prostate Cancer Symptom Scale (PCSS), before the visit. The specific symptoms were discussed with the patients. All symptoms were classified according to the Common Toxicity Criteria (CTC) scale 4.0 when applicable.

The presence of lower extremity lymphedema was examined by a physiotherapist, specialised in lymphedema following a protocol including measurements of limb volume and local tissue water, palpation and questions on symptoms related to lymphedema. A geometric volume method was used to determine limb volume. Local tissue water was evaluated with a device that transmits an ultra-high frequency electromagnetic wave of 300 MHz into an open-ended coaxial probe in contact with the skin. Based on these measurements, the tissue dielectric constant (TDC) was calculated, directly proportional to the tissue water content.

The number of patients in this study was small, which provided the opportunity to carry out qualitative research, which is very time consuming. The results from such a study are primarily hypothesis-generating, and must be confirmed in larger studies. A group of patients that had undergone extensive treatment was studied so that the results could be used to create a questionnaire for a larger group of patients. The CTC rating was used in order to be able to compare the results with those from other studies. The disadvantage of using CTC to classify limb edema

is that the difference in limb volume is a criterion, which could also be affected by cardiovascular comorbidity and overweight. Using the physician's (or physiotherapist's) assessment would have been less objective but may have led to more accurate selection of the true positive cases. An electrical device was used to measure the tissue water in an attempt to objectify the oedema. Another method of classifying edema is to use data from PROMs to reflect how the patient perceives his ailments.

Retrospective follow-up and dose–response analysis of patients treated with LDR at Skåne University Hospital

The patients in this study were men with low-to intermediate-risk disease treated before 2008 with LDR-BT without hormonal treatment, in the Southern healthcare region: in total 195 patients (Paper II).

The prescribed dose to the prostate was 145 Gy. The patients were followed systematically with respect to side effects for at least one year. PSA levels were obtained from medical records starting three months after the date of implant and for at least five years. Biochemical failure was defined according to the Phoenix definition, i.e. PSA at nadir + 2 ng/ml. The primary endpoint was time to biochemical failure. The outcome was analysed in relation to clinical variables at baseline and to RT data.

Statistical analysis was performed using the Kaplan–Meier method to estimate biochemical failure-free survival (BFFS), and Cox regression for univariable and multivariable analyses to identify and assess predictive clinical and treatment-related factors of biochemical failure. Multivariable analysis was carried out with only two covariates, bearing in mind the limited number of events. The combination of $D_{90\%}$ and PSA was chosen based on presumed causality and the results from univariable analyses.

The advantage of studying results from patients treated at our own hospital is that we have easy access to patient records and treatment planning information for the follow-up. A disadvantage is that the results from may not be generalised to other clinics with different treatment routines. A retrospective follow-up is valuable for one's own clinic, to confirm that the results of treatment are as expected, but also for the wider community when there is a shortage of randomised studies. The side effects in this study were not classified according to a standard scoring system

which is a disadvantage. A control group would have been desirable and attempts were made to find a matched population treated with EBRT. Unfortunately, the follow-up procedures were not comparable.

ED after EBRT – Dose–response analysis of patients from a randomised multicentre UHF study

Patients included in the HYPO-RT-PC trial randomised to CF (39x2.0 Gy, over 8 weeks) or UHF (7x6.1Gy, over 2.5 weeks) with no ADT were studied (Paper III). Only men with a sufficient erectile function for intercourse at baseline and complete RT data were included, thus 673 out of the 1180 patients in the per-protocol population.

RT was administered with three-dimensional conformal radiation therapy (3D-CRT) (80%) or VMAT (20%) using image guidance based initially on the BeamCath® technique (10%) and then implanted fiducial markers (90%). For the UHF patients treated with the BeamCath® technique all fractions were given with BeamCath® using small (4-6 mm) CTV-PTV margins. For the CF patients only four fractions were given with this technique while the remaining 35 fractions were delivered with wider margins and no IGRT (image-guided radiation therapy). For the patients treated with fiducial markers, an isotropic CTV-PTV margin of 7 mm was used in both treatment arms.

Patients were followed up at end of RT, at three, six, nine and 12 months after the start of RT and then every six months. At these visits erectile function was assessed as: “sufficient for intercourse”, “not sufficient for intercourse” (moderate ED) or “severe erectile dysfunction” (severe ED).The PB and crus were retrospectively delineated on the treatment planning CT scans.

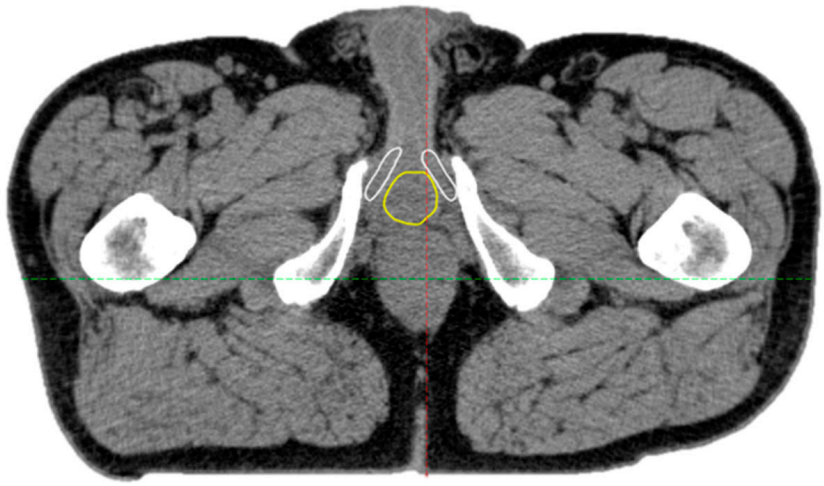

Figure 3. CT image at the cranial part of the PB with segmented penile bulb and crus. (From Paper III, reprinted with permission from Elsevier.)

Dose-volume descriptors were derived from EQD2-converted dose matrices (α/β=3 Gy). Statistical analyses were carried out using uni- and multivariable Cox proportional hazard regression and logistic regression in order to find predictors for ED. The time-to-event analysis was also performed using hormonal treatment and death as competing events.

The advantages of using patients from a large multicentre study is that the patients are defined according to the specific inclusion criteria, follow-up is systematic and site-specific deviations are accounted for. The results should therefore be more easily transferrable to the wider community. The patients were randomised which is a considerable advantage when comparing the two treatment arms. The two vastly different fractionation schedules could be a drawback, and it was necessary to rely on the validity of the LQ-model for transformation of the physical dose distributions to EQD2 doses based on an adopted value of α/β. On the other hand, clinical data from UHF treatments are of great interest in the RT community as there is a demand for results using these new fractionation schedules

ED is a very difficult endpoint to classify and there is no objective method of measuring it. We had access to the physician's assessment and PROMs from a

quality of life questionnaire (PCSS). PROMs were not included in the analysis for several reasons. The main reason was that time-to-event analyses were primarily performed in order to gain an understanding of the development of ED after RT. For these analyses two consecutive follow-ups or more were required, without later recovery, for defining an event. The PROMs were performed on fewer occasions with an increasing number of dropouts at each follow-up occasion. Furthermore, PROMs data are ordinal, and were therefore not directly suitable for this approach. There was also a discrepancy between the baseline ED reported by the physician and in the PROMs in about 10% of the included patients. The physician's assessment of ED is based on a verbal statement by the patient and may be influenced by both the patient and investigator. The use of a more internationally accepted scoring system in the HYPO-RT-PC trial for ED reported by the physician, such as CTCAE, may have been better. In some studies on ED, the International Index of Erectile Function (IIEF), has been used, which has the advantages of being validated and well known, but includes other aspects of sexual function as desire and satisfaction. This might be valuable when studying sexual dysfunction but may obscure the results when analysing dose-response for the endpoint ED.

Hip complications after EBRT – Dose–response analysis in patients with long follow-up using national registers

This study was carried out on 349 patients with prostate cancer treated to curative dose (≥64 Gy) with EBRT during 1997-2002 in Umeå (Paper IV). All patients were treated with 3D-CRT. The femoral heads, pubic arch and sacrum were delineated as OAR. Dose-volume descriptors were derived for these OARs.

ICD codes, were used to collect information on skeletal events for the patients, and 1661 matched controls through the Prostate Cancer data Base Sweden (PCBaSe), a national database for clinical epidemiological research

The statistical methods used were uni- and multivariable Cox proportional hazard regression (HR), to analyse time to events. In addition to cause-specific HRs, subdistribution HRs were calculated with death and bone metastases as competing events.

The advantage of using this group of patients were that 3D dose distributions were available and the follow-up time was long. Registers are convenient for long-term follow-up, but suffer from the drawback that the data are not monitored. As ICD codes are used for financial allocation, this information is probably of good quality but other variables found in registers may be subject to greater uncertainty.

Results and Discussion

Low rate of lymphedema after extended pelvic lymphadenectomy followed by pelvic irradiation of node-positive prostate cancer

The median follow-up time was 2.2 years (range 1.2-4.1). Half of the patients were receiving hormonal therapy at the time of examination. Their disease was under good biochemical control with PSA ≤0.1 in 64% and PSA <1 in all of the cases. None of the patients showed any clinical signs of prostate cancer. Lymph node dissection included a maximum of 39 dissected nodes and more than 20 nodes were dissected in seven patients (Paper I).

Lymphedema and other limb symptoms

Six patients (27%) experienced grade 1 lymphedema and two patients (9%) grade 2 while none had grade 3 or 4 according to the CTC scale 4.0. Two patients had been using compression stockings before the visit, and one patient was diagnosed with lymphedema requiring treatment, and was provided with compression stockings at the time of examination. More than 50% of the patients reported on one or more symptoms in the legs, such as swelling and pain. No correlation was found between the reported RT volumes and lymphedema or between the number of nodes dissected and lymphedema.

Other side-effects

Genitourinary and gastrointestinal side effects were common but usually mild, i.e. CTC grades 1-2. One patient had faecal incontinence of CTC grade 3. Over 70% of the patients had severe ED (CTC grade 3). One patient reported pelvic pain (CTC grade 3). This was a patient with multiple fractures in the pubic bone. The same patient had also lymphedema CTC grade 2. This patient had been diagnosed with osteoporosis and fractures before treatment for prostate cancer and reported unilateral ankle swelling already after lymph node dissection. Fourteen patients

(64%) reported only very mild side effects (CTC grade 1) apart from ED. Cardiovascular disease was common (in about 60%). The majority of the patients were physically very active.

Discussion

This study of 22 patients with high-risk nodal-positive disease, treated with extensive surgery followed by RT and ADT, showed that most patients had only mild and manageable late side effects, apart from ED which is an expected side effect of this combination of therapies. As the level of late toxicity was acceptable, this local treatment is deemed appropriate for patients in good clinical condition.

The extent of surgery and the irradiated volumes probably influence the risk of lymphedema. The majority of these patients had undergone extended pelvic lymph node dissection according to general guidelines, described in the background, and no correlation was found between the number of nodes dissected and lymphedema. Nether was any significant relationship found between segmented pelvic nodal volumes or treated/irradiated volumes and lymphedema. This was not surprising as the number of patients was small. However, it should be noted that in three cases the nodal target volume was delineated far more caudally than the RTOG recommendations and these patients were all diagnosed with lymphedema.

A larger study with longer follow-up is required to allow the analysis of the dose–response relationship and draw more reliable conclusions. It is difficult to obtain reliable information on lymphedema without a clinical examination, as many patients report symptoms in the legs, such as swelling and pain, without any signs of lymphedema. A larger study would be rather time consuming but might be possible if patients were selected based on PROMs.

Low-dose-rate brachytherapy with I-125 seeds has an excellent 5-year outcome with few side effects in patients with low-risk prostate cancer

The Kaplan–Meier-estimated median follow-up time for the LDR-BT patients was 6.2 years. At five years, 23 patients had biochemical recurrence, according to the Phoenix definition, but 14 of these patients were classified as bounce*, leaving nine patients with true recurrence of disease (4.6%), and 191 patients free from

disease (91.2%); eight patients lost to follow-up (4.1%). The Kaplan–Meier estimated BFFS at five years was 95.7% (Paper II).

Dose–response

$D_{90\%}$ was found to be a significant predictor of biochemical failure, BF: (HR=0.90 [95%CI 0.83-0.96], p=0.002). The only other variable that contributed significantly in the multivariable analysis was PSA before treatment; the higher the PSA level, the higher the risk of relapse. ROC (receiver-operating characteristic) curve analysis and Cox proportional hazard analysis of the most significant split between the Kaplan Meyer curves for BFFS suggested an optimal cut-off level of 167 Gy.

There was a tendency towards better outcome in the patients treated towards the end of the study period. $D_{90\%}$ was significantly correlated to treatment year showing increasing doses with time.

Side effects

The patients' mean self-reported International Prostate Symptom Scores (IPSS) and "urinary bother" (last question on the IPSS form) were elevated at three months, but had decreased at one year, almost reaching the baseline. The same effect was seen for maximal urinary flow rate, which was decreased at three months (Figure 4). Almost half of the patients reported urinary urgency (without specification) after three months. This number decreased to 20% after one year. Urinary incontinence was rare. No correlation was found between the absorbed dose measured as $D_{90\%}$ or urethra $D_{30\%}$ and GU side effects.

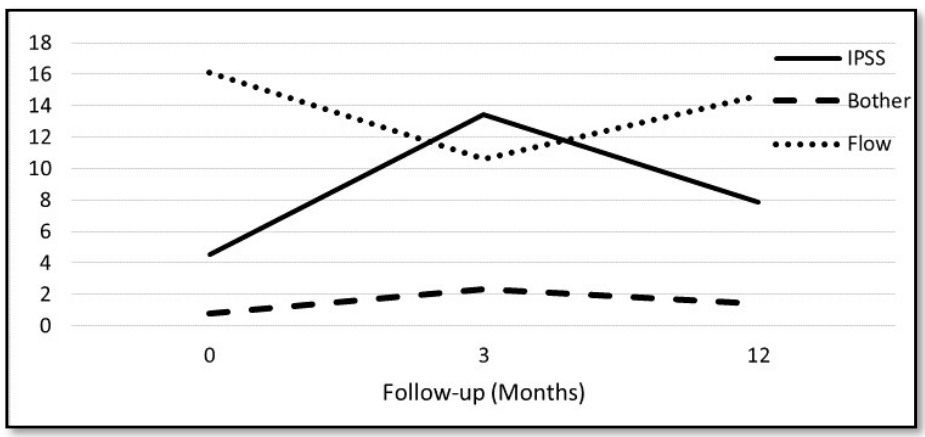

Figure 4. Mean values of IPSS (0-30), urinary bother (0-6) and urinary flow (ml/min).

About 10% of the patients treated with LDR-BT reported gastrointestinal side effects after 3 months, without further specification. The frequency of this problem had decreased to 4 % at the one-year follow-up.

No correlation was found between $D_{90\%}$ and ED, but information on baseline ED was missing for more than 40% of the patients and ED was not graded. Of the 83 patients without ED before treatment 61% still had no ED at the 1-year follow-up. Patients using PDE5i were classified as having ED.

Discussion

This second study involved patients undergoing LDR-BT for the treatment of low-risk prostate cancer. The BFFS at 5 years was 95.7% and a significant association was found between dose and tumour control. A high BFFS is expected for this group of patients. The strongest predictor of BFFS was $D_{90\%}$ which also remained significant in multivariable analysis. It should be noted that during the treatment period in this study, including the start-up, a significant trend towards better results concerning BFFS was observed. This could be considered a learning effect, and is probably mostly dosimetric, since dose to prostate ($D_{90\%}$) also increased. However, there may be other explanations. The physicians performing the procedure became more experienced and the selection of patients may have slightly shifted.

The biopsies from all patients except one showed a Gleason score ≤6 and 90% had low-risk disease when including PSA and stage. AS is usually the standard of care today for low-risk patients; EBRT, RP or LDR-BT being alternatives. At the time when these patients were treated they were all considered suitable for definitive treatment. Today, LDR-BT is recommended for low-risk (and selected intermediate-risk) patients who need or request active treatment. A practical advantage of LDR-BT is that the patient requires a hospital stay of only one day, and may then return to normal life.

Toxicity during the first year was deemed to be acceptable, with an increase in GU at three months, in line with similar studies with a long follow-up. A longer follow-up using a validated scoring system would have been needed to explore any dose–response associations regarding toxicity. Anyhow, the outcomes were excellent and support LDR-BT as a treatment alternative to selected patients.

*Bounce: A temporary increase in PSA of more than 0.2 ng/ml above the nadir with a subsequent return to the pre-bounce level, or to below 0.5 ng/ml

Erectile dysfunction and absorbed dose to penile base structures in a randomised trial comparing ultrahypofractionated and conventionally fractionated radiotherapy for prostate cancer

The patients included in this study were those without ED at baseline and available dose plans. In total, 673 patients were included (330 and 343 in the CF and UHF arms, respectively), i.e. 57% of the 1180 per-protocol patients in the trial (Paper III).

A strong correlation was found between the dose-volume descriptors studied ($r>0.85$) for both the PB and crus. A strong correlation was also found between the dose distributions in the PB and crus ($r>0.8$). Dose–response analyses were therefore restricted to the PB.

Average value (EQD2 corrected using $\alpha/\beta=3$) of D_{mean} in the PB was 24.5 in CF and 18.7 Gy in UHF, respectively. The corresponding values for the average value of $D_{2\%}$ were 52.1 in CF and 46.0 Gy in UHF. The EQD2 doses were consistently lower in patients in the UHF group than in the CF group, primarily due to the linearly scaled dose-volume objectives/constraints but also due to the differences in margins in the patients treated with Beam Cath®.

Frequency of ED

Severe ED occurred in 181 (27%) patients during the follow up period (89 (27%) in CF- group and 92 (27%) in the UHF-group). Severe ED was present in 74 (11%) (37 in each treatment arm) at 12 months and in 105 (18%) (53 in the CF-group and 52 in UHF-group) at 24 months.

Severe/moderate ED occurred in 340 (51%) patients during the follow up period (166 in CF-group (50%) and 174 in UHF-group (51%)).

Time-to event analyses

No significant difference was seen in the development of ED (severe or moderate) over time between the CF and UHF groups. For the whole study population the only statistically significant predictor in the Cox analyses was age, in both univariable and multivariable analyses. Of the dose-volume descriptors tested, $D_{2\%}$, was the strongest predictor of time to severe ED ($p=0.08$). Further analyses showed that the association between dose and severe ED was strongest for the

younger patients in the study cohort. A strong significant association between dose and severe ED was found in those aged 65 years or and younger.

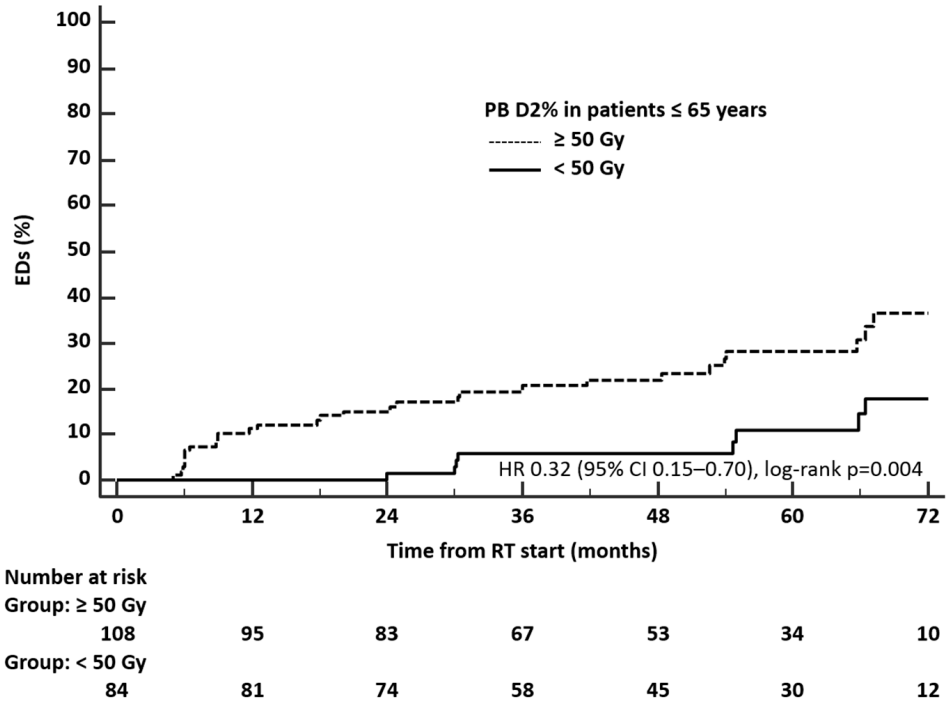

Figure 5. Cumulative incidence of severe ED for D2% to the PB less than or greater than 50 Gy in patients aged 65 years or younger. (From Paper III, reprinted with permission from Elsevier).

Severe ED at 12 and 24 months

All dose-volume descriptors studied were significantly associated with severe ED in univariable logistic analysis at 24 months, but only $D_{2\%}$ was significantly associated with severe ED at 12 months; the strongest single dose predictor at both follow-up times. In multivariable analysis, age together with $D_{2\%}$ were significant predictors of severe ED at both 12 and 24 months.

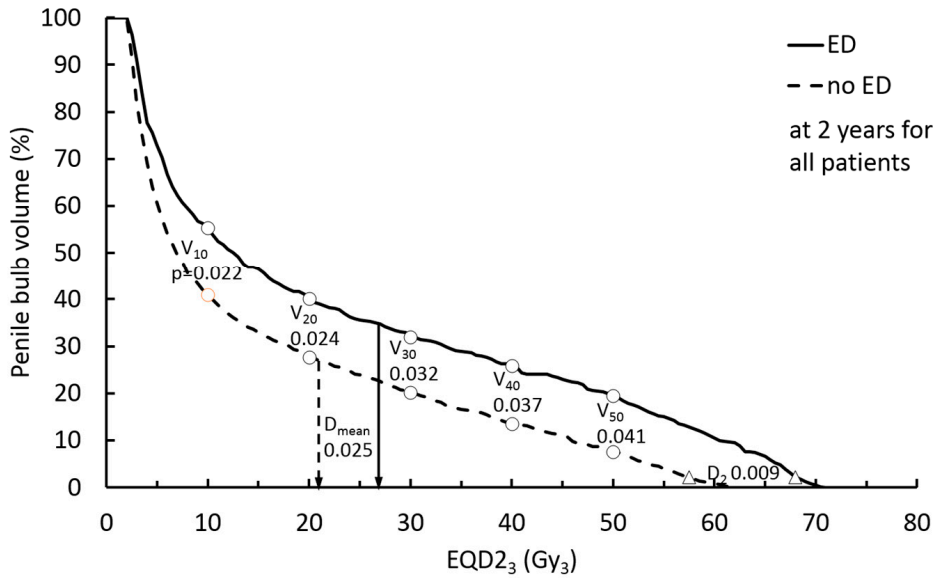

Figure 6. Median dose-volume histograms for patients with and without severe erectile dysfunction at two years.EQD2 corrected doses using α/β=3. (From paper III, reprinted with permission from Elsevier).

A strong significant association between dose and severe ED was found at both 12 and 24 months for the younger patients. As in the case of the whole patient group, $D_{2\%}$ was the strongest dose predictor of severe ED for those aged 65 years or and younger.

The best cut-off values predicting severe ED were 50 Gy for $D_{2\%}$ and 20 Gy for D_{mean} at both 12 and 24 months (Figure 7).

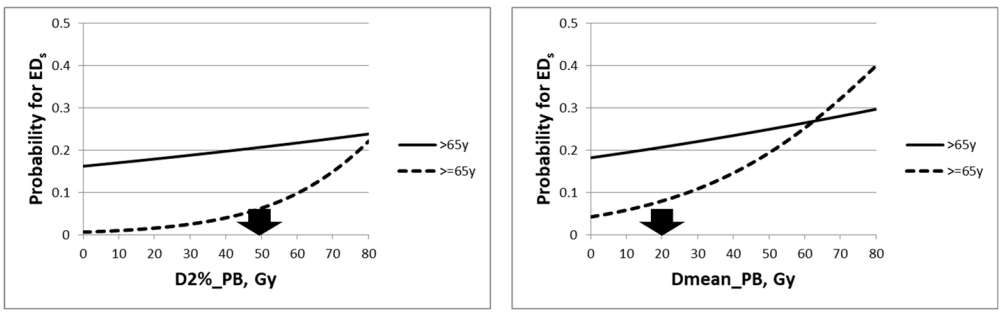

Figure 7. Risk of severe erectile dysfunction versus $D_{2\%}$ and D_{mean} at 2 years for patients younger and older than 65 years. The recommended cut-off values are indicated by the arrows.

Image-guided radiotherapy

When further analysing the data, a statistically significant difference in severe ED was found between the CF patients treated with BeamCath® and those treated with fiducials as image-guidance (p=0.006). This supports an association between absorbed dose and severe ED as the DVHs (dose-volume histograms) differ considerably when using the BeamCath® technique in the CF-patients due to differences in the CTV-PTV margins.

Discussion

In this study the risk of ED in patients treated within the HYPO-RT-PC trial, the first published prospective randomised phase III study comparing CF RT with UHF RT, was evaluated. The main focus was on the impact of radiation doses to the penile base. The results showed that age at RT is the strongest predictor of ED followed by the "near maximum" dose ($D_{2\%}$) to the PB. However, all the dose-volume parameters studied were significantly associated with severe ED at 24 months. This implies that dose-volume parameters other than $D_{2\%}$ could also be of importance when defining treatment planning dose-volume objectives for the PB.

We found that the best cut-off dose to prevent severe ED was at a near-maximum dose of 50 Gy to the PB, based on results for younger patients (≤65 years). In addition a mean dose of 20 Gy is suggested as a dose volume objective for the PB. These values can be compared to the recommendation made by the QUANTEC group, i.e. to limit the mean dose to the PB below 50 Gy (to 95% of the volume). The QUANTEC recommendation is based on the result of only a few studies. The largest study included (in which the dose–response association was evaluated) was carried out on 158 patients (77), where the mean dose to the PB was higher than in the present study (Paper III). The low mean dose in the present study could explain why the near-maximum dose ($D_{2\%}$) was a better predictor of ED than the mean dose, and also why the dose–response relationship was quite weak. The highest dose, probably most important for side effects, is received by the upper part of the PB, and reflects the doses in the surrounding tissues including the crus. On the other hand D_{mean} might be less sensitive to delineation. The cranial part of the bulb will have a major impact on $D_{2\%}$. Recently presented dose-ED results for 233 patients without severe ED at baseline, treated within the CHHiP trial showed that a mean PB dose <20 Gy increased potency preservation, supporting the findings of the present study.

The frequency of ED and its development over time in the present study was similar in the CF and UHF groups despite the fact that $EQD2_3$–corrected doses

to the erectile tissue were, as expected, lower in the UHF group. A complementary analysis with $EQD2_2$ correction (using α/β= 2 Gy) resulted in more similar dose distributions to the PB in the two groups. This could indicate that the value of α/β for the tissues involved in the pathogenesis of radiation-induced ED is less than 3 Gy, indicating radiation injury to slow-reacting structures, such as nerves and vessels.

This study is the largest study to date on the effects of dose on ED, and is unique as patients treated with UHF RT are included. It therefore provides important contributions to our knowledge in the field.

Long-term risk of hip complications after radiotherapy for prostate cancer – A dose–response study

Of the 349 patients included in this study, data were missing for three patients in the PCBaSe, leaving data from 346 patients for analysis. The median follow-up time was 16.0 years (Paper IV).

The median average physical dose and the corresponding equivalent 2-Gy/fraction dose to the femoral heads were Davg = 35.5 Gy and EQD2avg = 28.7 Gy, respectively. The corresponding median near-maximum doses were $D_{2\%}$ = 43.6 Gy and $EQD2_{2\%}$ = 36.9 Gy, respectively. During follow-up, a total of 20 fractures occurred, 12 of which were hip fractures. Hip osteoarthritis was diagnosed in 36 cases; 29 cases leading to replacement surgery.

No increased risk of hip fractures was found in the irradiated cohort compared to the control group. Hip osteoarthritis was the only event for which a statistically significant difference was found between the irradiated cohort and the controls (cause-specific HR 1.56 (95%CI: 1.07-2.26, p=0.02)). When analysing the data using death and bone metastases as competing risks, the subdistribution HR was 1.44 (95%CI: 0.99-2.09, p=0.055). The cumulative incidence of osteoarthrosis at 10 years was 8.1% (95%CI 5.2-11.0) and 4.9% (95%CI 3.9-6.0) in the irradiated cohort and in the controls, respectively.

A statistically significant relationship was found between osteoarthritis and the volume of the femoral head receiving an EQD2 dose of ≥40 Gy,$V_{EQD2\ 40Gy}$, (unadjusted HR=1.094, 95% CI 1.041-1.149, p<0.001) (Figure 8). The cut-off dose of EQD2=40 Gy is close to the maximum dose in the material, hence a large proportion of the patients (77%) had maximum doses lower than 40Gy (V_{EQD2}

$_{40Gy}$ = 0). When all patients with $V_{EQD2\ 40Gy}$ = 0 were excluded, leaving 81 patients in the analysis, a HR of 1.10 (95%CI 1.031-1.17 p=0.003) was obtained.

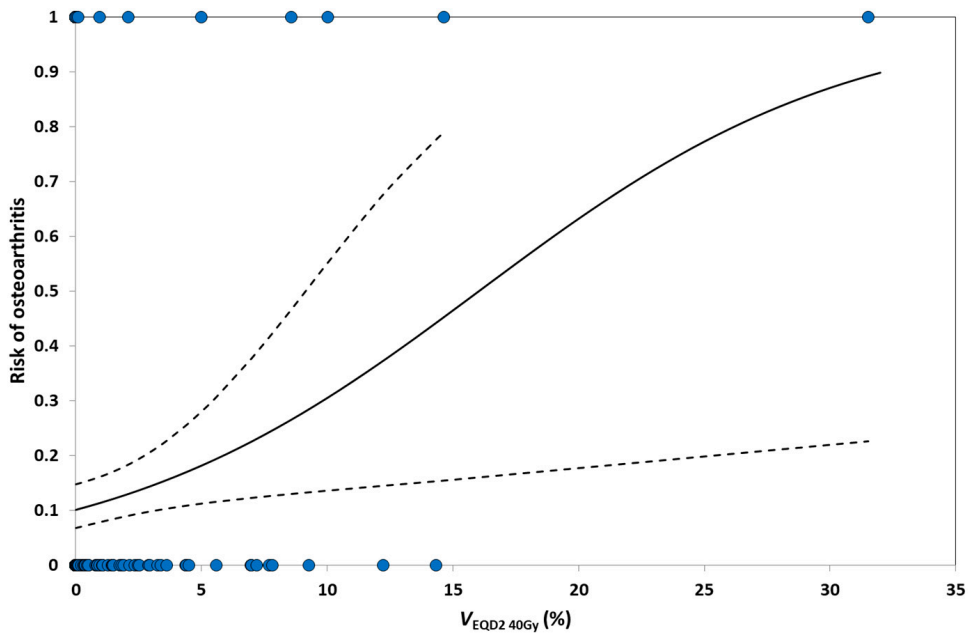

Figure 8. Risk of osteoarthritis within 10 years after radiotherapy vs, $V_{EQD2\ 40Gy}$ (solid line) with 95% confidence intervals (dashed lines).

Discussion

No increased risk of hip fracture was found in the irradiated cohort compared to the matched controls, after a median follow-up time of 16 years. The only complication that was significantly worse in the irradiated cohort compared with the control group was hip osteoarthritis. This finding is clinically relevant, as 80% of patients diagnosed with osteoarthritis required hip replacement. The median time to hip osteoarthritis was 7.9 years. This finding is in line with that by Zelefski et al. (91), who reported a low incidence of long-term hip-related toxicity after a median follow-up period of seven years.

The only dose–response combination found to be statistically significant was between $V_{EQD2\ 40Gy}$ and hip osteoarthritis, although the confidence interval was wide (Figure 8). This dose–response relationship must thus be confirmed in other studies before it is recommended as a dose-volume objective in the clinic. To the

best of the author's knowledge no dose-volume objectives have been published for the endpoint osteoarthritis.

Apart from the low absorbed doses to the hip mentioned above, other limitations of this study are associated with the information available in the various national registers, as discussed above. Including the femoral neck in the delineation (according to the RTOG (25)) would have improved this study as this is the most common fracture site.

The patients in this study were treated with CF 3D-CRT. Nowadays most patients with prostate cancer are treated with (hypofractionated) VMAT, which may lead to higher doses to the femoral heads. In addition, pelvic lymph nodes are sometimes included, which also affects the absorbed dose to the hip. Further studies should include patients treated with contemporary RT techniques to allow more reliable dose-volume objectives to be determined for use in the clinic.

Conclusions

The main conclusions drawn from the work presented in this thesis are given below.

- There was a low incidence of lymphedema in patients with high-risk node-positive prostate cancer who have undergone pelvic lymph node dissection followed by HDR-BT and pelvic EBRT (Paper I).
- Most patients treated with this combination therapy experienced low overall toxicity, supporting the use of large pelvic fields for patients with high-risk node-positive prostate cancer (Paper I).
- The absorbed dose is a predictive factor for BFFS for low-risk patients without ADT, treated with LDR BT as unimodal treatment (Paper II).
- With the treatment routines and dosimetry used, a value of $D_{90\%}$ in the range of 170-180 Gy gives excellent outcomes for patients with low-risk prostate cancer (Paper II).
- The frequency of severe ED is similar in groups treated with CF RT and UHF RT (Paper III).
- Age at RT was the strongest predictor of severe ED, followed by dose to the PB, being most evident in younger patients (Paper III).
- Values of $D_{2\,\%} < 50$ Gy and $D_{mean} < 20$ Gy to the PB are proposed as primary objectives in the treatment planning process (Paper III).
- There is no increased long-term risk of hip fracture, but an increased risk of clinically relevant osteoarthritis after EBRT with CF RT, when mean dose to the femoral head is 35.5 Gy (Paper IV).
- There is possibly a dose–response relationship between osteoarthritis and the volume of the femoral head receiving an EQD2 dose of 40 Gy or higher (Paper IV).

Future Perspectives

A larger study on patients with limited lymph-node positive prostate cancer to compare tumour control and side effects (e.g. lymphedema and GI toxicity), with and without pelvic EBRT and including dose-response analysis, is desirable. A study of late toxicity after LDR-BT on all patients in Sweden treated with this technique, using PCBaSe, was intended to be included in this thesis but is not yet realised. The role for BT in the era of hypofractionation is challenged, so information on late toxicity after monotherapy BT is interesting especially if it can be compared to toxicity after (UHF) EBRT or RP.

The objectives used in RT planning must be continuously evaluated as treatments and dose planning tools evolve. Endpoints other than ED, such as GI-toxicity (e.g. rectal bleeding) and GU-toxicity (e.g. urethral stricture) remain to be studied following UHF treatment. Much work remains to be done in defining OAR for the investigation of complex side-effects such as ED. The PB and crus were studied in the present work, but other OAR, such as the prostate plexus (including the nerve bundles) and internal pudendal arteries (IPAs) would be interesting subjects of study. Based on the result of some pilot patients we believe that these OAR could be delineated using standard MRI with slightly modified sequences.

The PCBaSe is a useful source of information on late toxicity. The suggestion that there is a dose–response relationship between osteoarthritis and the volume of the femoral head receiving an EQD2 dose of 40 Gy or higher, should be confirmed in a larger study. A suitable clinical study could be performed on patients treated with contemporary technique such as IMRT/VMAT at our clinic, or at other Swedish radiotherapy units, with a follow-up period of ten years or more.

Finally, a dream is that studies of dose–response analyses should be considered in the planning phase of new radiation studies so that robust endpoints and follow-up for this purpose can be secured.

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